Insulin Management and Metabolic Control of Type 1 Diabetes Mellitus in Childhood and Adolescence in 18 Countries

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Insulin regimens and metabolic control in children and adolescents with Type 1 diabetes mellitus were evaluated in a cross-sectional, non-population-based investigation, involving 22 paediatric departments, from 18 countries in Europe, Japan, and North America. Blood samples and information were collected from 2873 children from March to August 1995. HbA_{1c} was determined once and analysed centrally (normal range 4.4–6.3 %, mean 5.4 %). Year of birth, sex, duration of diabetes, height, body weight, number of daily insulin injections, types and doses of insulin were recorded. Average HbA_{1c} in children under 11 years was 8.3 ± 1.3 % (mean ± SD) compared with 8.9 ± 1.8 % in those aged 12–18 years. The average insulin dose per kg body weight was almost constant (0.65 U $kg^{-1}24\ h^{-1}$) in children aged 2–9 years for both sexes, but there was a sharp increase during the pubertal years, particularly in girls. The increase in BMI of children with diabetes was much faster during adolescence compared to healthy children, especially in females. Sixty per cent of the children ($n = 1707$) used two daily insulin injections while 37 % ($n = 1071$) used three or more. Of those on two or three injections daily, 37 % used pre-mixed insulins, either alone or in combination with short- and intermediate-acting insulin. Pre-adolescent children on pre-mixed insulin showed similar HbA_{1c} levels to those on a combination of short- and long-acting insulins, whereas in adolescents significantly better HbA_{1c} values were achieved with individual combinations. Very young children were treated with a higher proportion of long-acting insulin. Among adolescent boys, lower HbA_{1c} was related to use of more short-acting insulin. This association was not found in girls. We conclude that numerous insulin injection regimens are currently used in paediatric diabetes centres around the world, with an increasing tendency towards intensive diabetes management, particularly in older adolescents. Nevertheless, the goal of near normoglycaemia is achieved in only a few. © 1998 John Wiley & Sons, Ltd.

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Abbreviations: BMI body mass index, DCCT Diabetes control and Complications Trial; ISPAD International Society of Paediatric and Adolescent Diabetes, SE standard error, SD standard deviation.

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Introduction

The Diabetes Control and Complications Trial (DCCT) Research Group has shown that most individuals with Type 1 diabetes mellitus in the 13–17-year-old age group would benefit from intensive diabetes management, in terms of reduction in the risk of onset and/or progression of early diabetes-related microvascular complications.[1] However, results from the adolescent cohort in the DCCT showed that intensive diabetes management, which produced a 1.5–2.0 % decrease in the mean HbA_{1c} levels, was associated with a 2–4 fold increase in the risk of severe hypoglycaemia, and significant weight gain.[1] Furthermore, HbA_{1c} levels were significantly higher in adolescents than in adults,[2] despite similar and extensive support from the multidisciplinary diabetes treatment team. Indeed, recruitment of adolescents able to follow an intensive management regimen was difficult, with an average of only three adolescents per centre in the intensive treatment group.[3] The American Diabetes Association points out that particularly in children and adolescents, it is important to devise an insulin regimen that is tailored to the individual's changing development and lifestyle,[4] taking into account the patient's capacity to understand and carry out the treatment regimen and the risk of severe hypoglycaemia. The risk of hypoglycaemia, resulting in unconsciousness or seizures, is greater with younger age (0–8 years) and lower HbA_{1c} level,[5–8] which calls into question the appropriateness of intensive insulin treatment in very young patients.

The Hvidøre Study Group on Childhood Diabetes examined blood glucose control in an international cross-section of children and adolescents.[9] This study showed that the mean HbA_{1c} (8.6 %, equivalent to 8.3 % in the DCCT) compared with the DCCT results in adolescents, in which the intensive treatment group had a mean HbA_{1c} of 8.1 % (versus 9.8 % in the conventional treatment group).[1] We were interested in examining the insulin regimens that were used in the Hvidøre study population to achieve this level of metabolic control. Here, we report on the insulin regimens and daily dosage in the children and adolescents participating in this study, and the various factors, such as age, sex, duration of diabetes, HbA_{1c}, injection frequency, and body mass index, which might have influenced their insulin regimens.

Methods

This multicentre, non-population-based, cross-sectional study involved 22 paediatric departments from 18 countries in Europe, Japan, and North America. Blood samples and information were collected from March to August 1995 on children and adolescents with Type 1 diabetes, born in 1977 or later and seen at the outpatient clinics during this period. The total of 2873 children included in the study represented approximately 70 % of all children and adolescents treated at the centres. There were 1443 boys and 1430 girls, with a median age of 13 years (range 1–18 years). Two blood samples were collected from each patient for HbA_{1c} determination. One was sent to the Steno Diabetes Centre (Denmark), the other was analysed locally. Year of birth, sex, year of diabetes onset, height, weight and insulin regimen (frequency of insulin injections, insulin dose and type) were also recorded.[9] The distribution of the individual insulin injections during the day and the specific pre-mixed insulin products, i.e. 10/90, 15/85, 20/80, 25/75, 30/70 40/60 and 50/50 (combined globally) were not recorded.

Samples for HbA_{1c} analysis were collected using the Bio-Rad HbA_{1c} Sample Preparation Kit (Cat. no. 196-1026, Bio-Rad Laboratories GmbH, Munich, Germany) and mailed to the laboratory as described.[9] HbA_{1c} results were found to be 0.3 % higher than the DCCT laboratory level by direct sample exchange. Body mass index (BMI) was calculated as weight divided by the height squared (kg m^{-2}). Age was calculated in calendar years. The international nature of this study precludes a detailed comparison with national standard growth charts. However, for general comparative purposes we have related the BMI for the study population to the published reference curves[10] for the UK 1990.

The study was performed according to the criteria of the Helsinki II Declaration and was approved by the Human Ethics Review Boards in each institution. All the patients and/or their parents/guardians gave informed consent.

Statistical Analysis

Summary statistics are expressed as mean ± SD or mean ± SE. Groups with less than five patients are not illustrated. Figure 1 is based on counts of patients in one-year age groups. Figure 2 is based on means in one-year age groups. Comparisons are based on normal distribution methods. Percentiles (Figure 3) are based on the empirical percentiles in each age group separately, using linear interpolation, where necessary. In Figure 6, patients not taking pre-mixed insulin, are grouped according to percentage of short-acting insulin, groups 0–10 %, 10–20 %, etc. Figure 7(a) shows the percentage using any pre-mixed insulin, among all patients. Figure 7(b) only considers patients on two daily injections with a diabetes duration above 2 years, using either only pre-mixed ($n = 379$), or only short and intermediate insulin ($n = 566$). The combined effect of insulin type and age, was evaluated in a multiple regression analysis, including gender and centre as class variables and duration as a linear variable.

Results

HbA_{1c} and Insulin Dose

The mean HbA_{1c} in the 2873 children was 8.6 ± 1.7 % (the equivalent of 8.3 %, DCCT). Values below 8.0 %

were observed in 34 % (747/2227) of the subjects who had had diabetes for at least 2 years. Figure 1 shows the age-related frequency distribution of the number of daily insulin injections in all participants. Most children aged under 9 years were on two (78 %) or three (13 %) insulin injections daily. Only a few children (7 %) received one insulin injection daily, and most of these had a very short duration of diabetes. In the adolescent group, the use of three and four insulin injections increased at the expense of two insulin injections per day. Only 10 children used an infusion pump. Six were not on insulin, presumably due to significant residual insulin secretion early in the course of their diabetes. In adolescents there was no significant relationship between HbA_{1c} and injection frequency. However, teenagers on four injections or more received significantly ($p<0.0001$) more insulin (0.11 ± 0.02 U kg^{-1} 24 h^{-1}) and the girls had significantly ($p<0.01$) higher BMIs (0.84 ± 0.26 kg m^{-2}) than adolescents on twice daily insulin.

Figure 2 illustrates the age-specific mean insulin dose (U kg^{-1} 24 h^{-1}) in all participants. The average insulin dose per kg body weight was relatively constant, at 0.654 U kg^{-1} 24 h^{-1}, particularly in girls between the ages of 2 and 9 years, but there was a sharp increase after 10 years. The highest mean insulin dose for girls was 0.98 ± 0.03 U kg^{-1} 24 h^{-1} at 14 years, after which the dose gradually decreased to 0.89 ± 0.03 U kg^{-1} 24 h^{-1} ($n = 77$) at age 18. The mean insulin dose of the boys increased gradually between 11 and 17 years to 0.98 ± 0.03 U kg^{-1} 24 h^{-1} and levelled at 0.95 ± 0.02 U kg^{-1} 24 h^{-1} at 18 years ($n = 85$).

Figure 3 shows the distribution of insulin dose by percentiles for girls and boys with diabetes duration of 3 years or more, thus excluding most children in the remission phase. The daily insulin dose showed considerable variation, fifth to ninety-fifth percentiles = 0.5–1.2 U kg^{-1} 24 h^{-1} among prepubertal girls and 0.4–1.0 U kg^{-1} 24 h^{-1} among prepubertal boys. This compares with 0.7–1.7 U kg^{-1} 24 h^{-1} among pubertal girls and

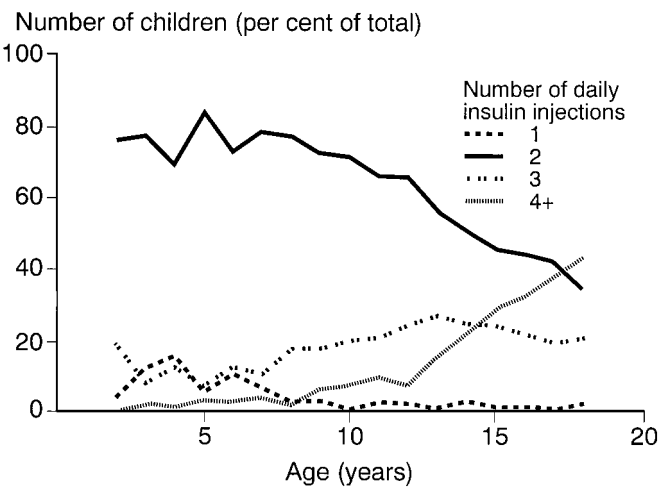

Figure 1. Age-related frequency distribution of number of daily insulin injections in 2857 children and adolescents with Type 1 diabetes mellitus

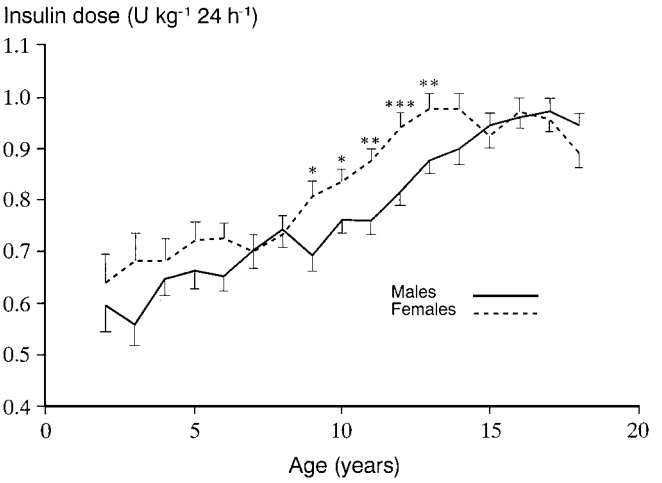

Figure 2. Age-specific mean values for insulin (U kg^{-1} 24 h^{-1}) in 1443 males and 1430 females with IDDM. The error bars represent 1 SEM value; *$p<0.05$; **$p<0.01$, ***$p<0.001$ in comparison of males and females separately in each age group

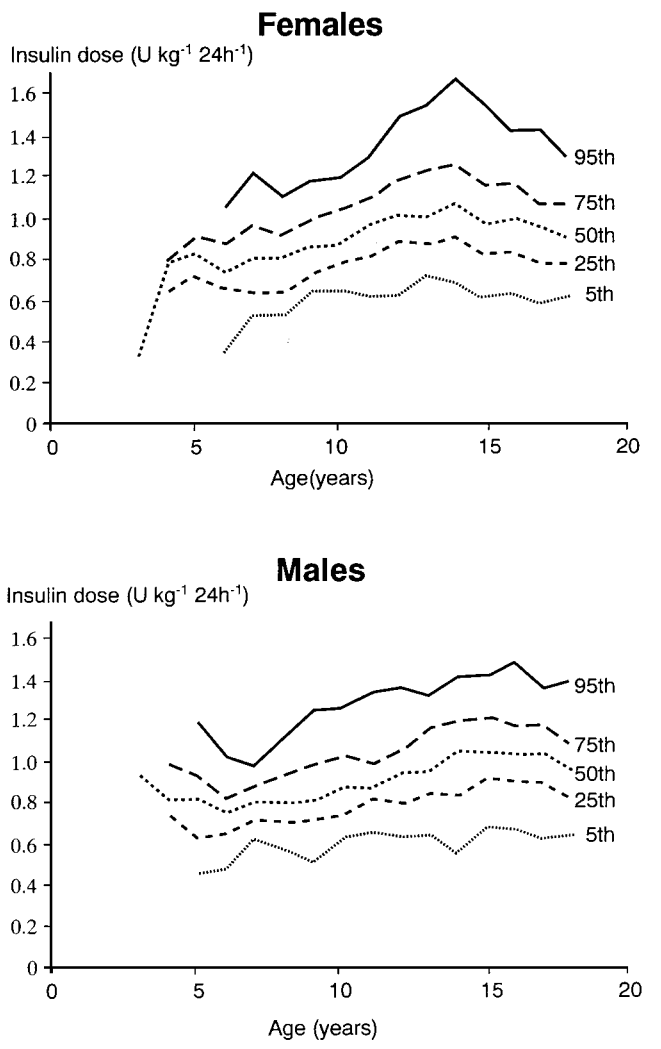

Figure 3. Distribution of insulin dose by percentiles for females (upper panel) and males (lower panel) with a diabetes duration of 3 or more years

0.6–1.5 U kg^{-1} 24 h^{-1} for pubertal boys. A total daily insulin dose higher than 1.0 U kg^{-1} 24 h^{-1} was seen in 50 % of pubertal subjects, compared with only 20 % of the prepubertal children. Insulin requirements and HbA_{1c} were significantly lower in patients with a disease duration of less than 3 years, due presumably to residual beta-cell function.

Body Mass Index

Age-specific median values for body mass index (BMI) for boys ($n = 1443$) and girls ($n = 1430$) with Type 1 diabetes mellitus, with healthy British girls and boys serving as a control group[10] are shown in Figure 4. In healthy controls, the changes in median BMI by age is very similar between the two sexes. The BMI declines and reaches a minimum at 5 to 6 years, when BMI is 15.5 kg m^{-2}. Subsequently BMI increases more rapidly in girls than in boys up to the age of 18 years when the curves meet. In the diabetic children, however, there is no decrease (the adiposity rebound) in BMI around 5 to 6 years (BMI 16.5 kg m^{-2}). The values for boys and girls are the same up to the age of 12 years but later diabetic girls increase more rapidly in BMI than diabetic boys. Compared with the control group, the BMI of diabetic children (especially females) continues to increase much faster during the teenage years. At 18 years the median BMI is 21.0 kg m^{-2} for healthy females and 23.5 kg m^{-2} for diabetic females. In contrast to healthy girls, females with diabetes continue to have markedly higher BMI than males at this age.

Insulin Types and Injection Frequency

To study the distribution of the ratios of short- and long-acting insulin types, those on pre-mixed preparations were excluded. The proportions of short- to intermediate-acting insulin in different age groups for patients on individual insulin combinations is shown in Figure 5. On average, the proportion of short-acting insulin was fairly constant (20 %) up to the age of 10 years, after which its use increased, reaching 50 % of 18-year-olds. In boys only, use of more short-acting insulin was associated with a significantly ($p<0.0001$, test for trend) lower HbA_{1c} level (Figure 6). When children on pre-mixed preparations were included (37 %) in the calculations we obtained practically the same result. In these calculations, those on pre-mixed preparations were assumed to use the predominant pre-mixed product, i.e. 30/70.

Table 1 shows the relationship between insulin types and injection frequency in 2857 children and adolescents with Type 1 diabetes. A mixture of short and intermediate acting insulin is the most often used combination in

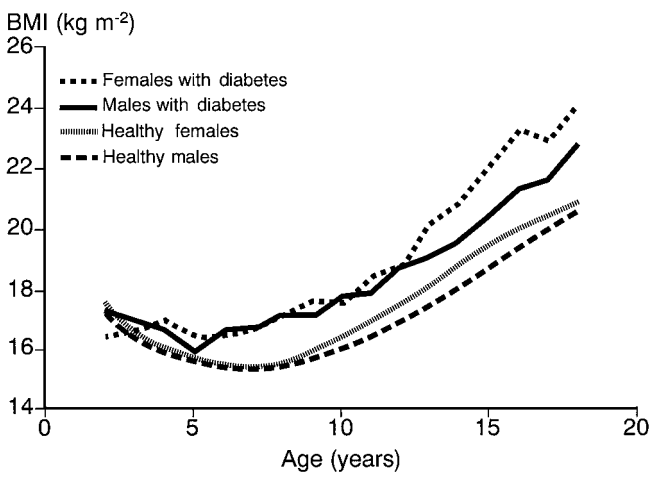

Figure 4. Age-specific median values for body mass index (BMI) in 1443 males and 1430 females with Type 1 DM with a group of healthy British children serving as controls

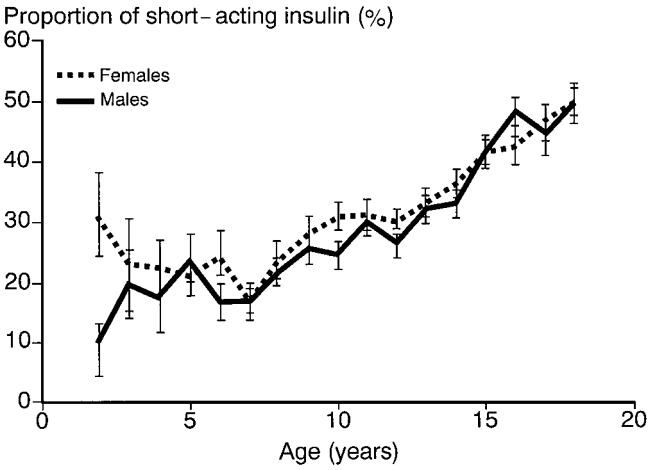

Figure 5. The proportion of short-acting insulin (%) in girls and boys on individual insulin combinations (2 to 4+ injections) related to different age groups. Average curves are shown for groups of more than five observations. The error bars represent 1 SEM value

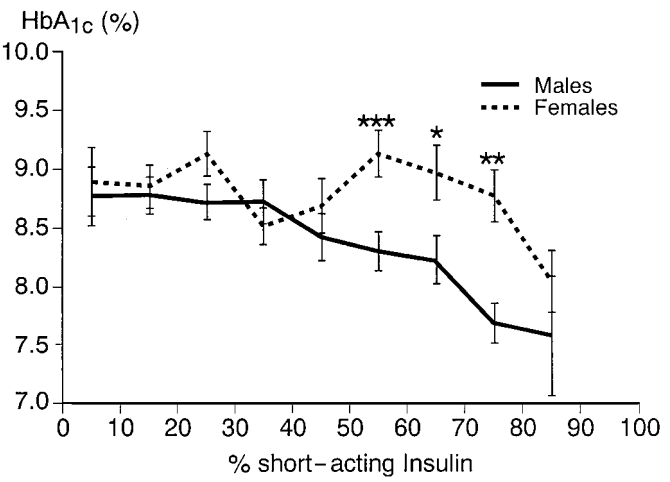

Figure 6. The relationship between HbA_{1c} and percentage short-acting insulin in males and females on individual insulin combinations (2 to 4+ injections). The error bars represent 1 SEM value; *$p<0.05$; **$p<0.01$, ***$p<0.001$ in comparison of males and females separately in each per cent short-acting insulin group

Table 1. The relationship between insulin type and injection frequency in 2857 children and adolescents with Type 1 DM

Insulin type	Number of daily insulin injections				Total
	1	2	3	4 or more	
Short and intermediate	25	901	366	447	1739
Pre-mixed	14	590	5	0	609
Short and pre-mixed	0	11	168	16	195
Intermediate	40	171	0	0	211
Other	0	34	42	27	103
Total number of patients	79	1707	581	490	2857

children on two, three or more insulin injections daily. Short and pre-mixed insulin, is mainly used in children on a three times daily regimen. When pre-mixed or intermediate insulin are given alone, this is almost exclusively in children on one or two injections per day. Other insulin combinations were used infrequently.

A pre-mixed form of insulin, either alone or in combination with short-acting and intermediate-acting insulin, was used in 37 % of the children on twice or three times daily insulin. Pre-mixed insulin was used both in the prepubertal years and during puberty (Figure 7(a)). There were no significant differences between the age-specific mean HbA_{1c} concentrations in children on twice daily pre-mixed insulin and children on twice daily short and intermediate acting insulin in the prepubertal years (Figure 7 (b)). Between 15 and 17 years, however, the adolescents on pre-mixed insulin had significantly ($p<0.05$) higher HbA_{1c} values compared with those on short and intermediate acting insulin (two injections per day).

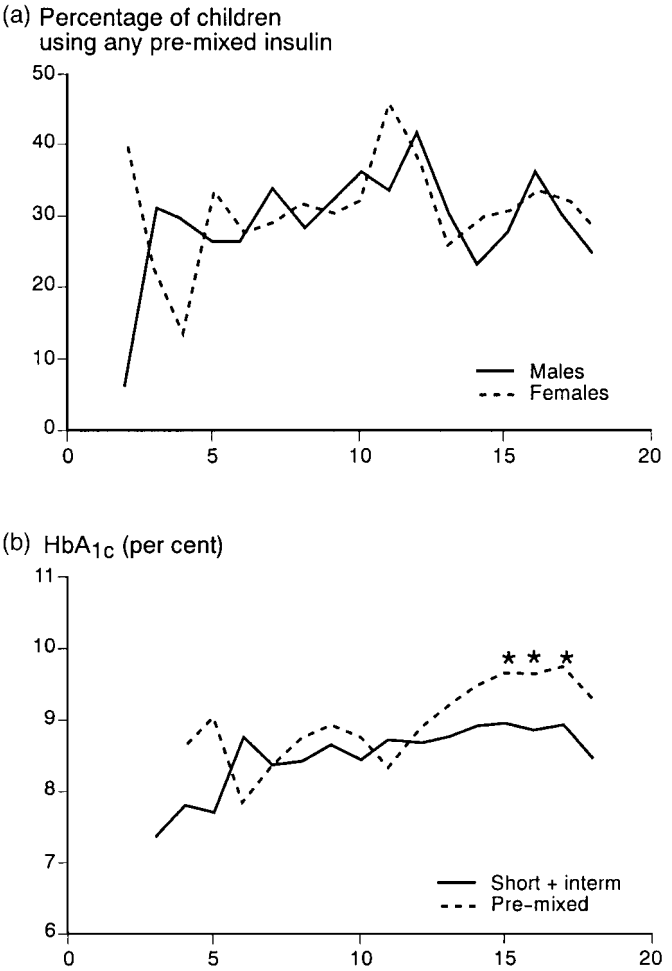

Figure 7. (a) The percentage of children using pre-mixed insulin related to age and (b) the age-specific mean HbA_{1c} concentration in children on pre-mixed ($n = 379$) vs short- and intermediate-acting insulin ($n = 566$) (two injections per day) adjusted for sex, duration, and centre effect; *$p<0.05$.

Discussion

In our survey of 2837 children and adolescents with Type 1 diabetes from 22 centres world-wide, we found that 41 % of those under 11 years old had an HbA_{1c} below 8.0 %, but only 29 % in the adolescent age group (12–18 years), despite the fact that 38 % of the latter were receiving three or more daily insulin injections—a similar proportion to the whole study population. In the younger age group, better glycaemic control was achieved even though many of these children received insulin only twice daily. This may be due to improved insulin sensitivity in these early years partly caused by reduced growth hormone secretion during the day. However, better compliance and lifestyle factors may also be involved; for example, in this age group, the child's parents are more likely to be responsible for giving the insulin injections and thus increasing compliance.

When the HbA_{1c} levels achieved by different insulin regimens in this study population were examined,[9] there was no significant difference in glycaemic control between adolescents receiving two, three, or four or more injections daily. However, adolescents on four injections or more received significantly more insulin and the girls had significantly higher BMI than adolescents on twice daily insulin. These findings suggest that variables other than injection frequency and dose (e.g. psychosocial factors, patient-education, and self-care behaviour) may be equally important in achieving satisfactory metabolic control.[11] Thus, the term 'intensified diabetes management' should not be interpreted simply as meaning frequent insulin injections. Equally, in setting up quality indicators for good glycaemic control, rates of severe hypoglycaemia should be taken into consideration[9] due to the harmful effects on neuropsychological intellectual function in children.

The average insulin dosage remained steady throughout childhood but increased rapidly after the onset of puberty. There was no significant difference in insulin dose between boys and girls until adolescence (11–18 years), when the insulin dose in girls was considerably higher than in boys (Figure 2). The average insulin doses seen

in these adolescents were comparable to those used in the adolescent group of the DCCT,[1] in which both treatment groups were receiving similar doses (1.0 U kg^{-1} 24 h^{-1} in the intensive treatment group and 0.97 U kg^{-1} 24 h^{-1} in the conventional treatment group).

There was a wide variation in the distribution of insulin dose plotted by percentile, in both sexes (Figure 3). The pattern of higher insulin dose in the pubertal years is again striking, with more marked increases in the higher percentiles, especially for girls. This increase in insulin requirement during puberty has also been shown by Dorchy *et al.*[11] and Kerouz *et al.*[12], again with girls needing higher doses than boys. The differential insulin requirement between girls and boys may be due, in part, to earlier age of onset of puberty in girls, but also to the differential effect of sex hormones on glucose homeostasis.[13,14]

Many health care providers believe that the total daily insulin dose in children should not exceed 1.0 U kg^{-1} day^{-1}, so that the proportion of children who were treated with an insulin dose above this is of interest. In fact, half of the pubertal and one-fifth of the prepubertal children exceeded this limit. These figures are slightly higher than those found by Kerouz *et al.*[12]

The unsatisfactory glucose control during puberty may be due to several factors, including decreasing compliance with different aspects of the treatment regimen[15,16] and decreased insulin sensitivity of peripheral tissues during adolescence[17–19] perhaps caused by hypersecretion of growth hormone.[20] This insulin resistance leads to increased insulin requirements[22], which may be at least partly responsible for the increase in age-related BMI in boys and girls seen both during the prepubertal and the pubertal period when compared to healthy control children.[10] The BMI of particularly the females with diabetes continues to increase during adolescence. This finding is in agreement with the results of a recent Danish nation-wide investigation.[21] It remains controversial whether multiple injection therapy *per se* is associated with weight gain. Some studies have shown a possible association,[1,9,11,22,23] while others dispute this.[24,25] Multiple daily injections mean more flexibility and the attitude of teenagers towards diet may become more relaxed on such intensive insulin therapy causing weight gain.

Insulin dose and HbA_{1c} increased gradually during the first 3–4 years of the disease and then reached a plateau. This finding might be explained by a persistent but decreasing endogenous insulin secretion in the early years after diagnosis.[26] An important observation from the DCCT study[27] was that beta-cell function seemed to continue for a longer period of time in the intensive treatment group compared to conventional treatment. It would be of interest to discover whether this beta-cell sparing is a feature of an intensive management regimen[28] and whether it contributes to better control and fewer microvascular complications.

Infants, toddlers and younger diabetic children on individual insulin combinations were treated with less short acting insulin compared to older children possibly because of residual beta-cell function or for fear of inducing severe hypoglycaemic attacks.[26] In addition the majority of children in the younger age group were treated with insulin twice daily. By contrast, in adolescence most patients were treated with three or more insulin injections daily and this may also explain the increased use of short-acting insulin in the older age group as these insulin regimens often are combined with use of more short-acting insulin.

Adolescent males treated with more daily units of short-acting insulin had significantly lower HbA_{1c} levels compared with those on more units of long-acting insulin. This association was not found in females, an observation perhaps partly explained by a sexual dimorphism in insulin sensitivity where adolescent females are more insulin resistant than males.[13] In a follow-up study of former DCCT participants[29] a higher bolus/basal insulin ratio correlated with lower HbA_{1c} values.

Most patients were on twice daily insulin—mainly a combination of short and intermediate acting insulin (Table 1). The high number of children on pre-mixed insulin in this study is in contrast with the recommendations from the International Society for Paediatric and Adolescent Diabetes (ISPAD) consensus guidelines,[30] in which pre-mixed insulin is discouraged for general use in childhood and adolescence 'because of changing needs in the ratios of the two types of insulin.' Pre-mixed insulin is commonly used in the prepubertal years (Figure 7), presumably due to its ease of use and the fact that many studies have failed to show significant differences between fixed insulin mixtures and variable mixtures.[31] Also, using pre-mixed insulin avoids the risk of errors when parents or the patients mix the insulins themselves. The glycaemic control in pre-adolescent children on pre-mixed insulin appeared to be comparable with those on a variable combination of short- and long-acting insulins. However, the potential benefit of individual self-adjustment of the ratio of short- and intermediate/long-acting insulin became apparent in the adolescent subgroup, where pre-mixed insulin was associated with significantly poorer control (Figure 7(b)). The better glycaemic control achieved in the younger age groups irrespective of insulin types may be due to improved insulin sensitivity and better compliance. In adolescence, however, there is a need for larger insulin dosage during the phase of rapid growth. In addition many teenagers have irregular diet and irregular activity during the day which needs individual self-adjustment of the ratio of short and intermediate acting insulin to match their lifestyle. This may explain why pre-mixed insulin was associated with significantly poorer control in the adolescent subset. However, in a recent short-term study O'Hagan *et al.*[32] reported that switching to pre-mixed insulin in children aged 7–16 years had no detrimental effect on glycaemic control.

Improvements in metabolic control[1] can be achieved by use of intensive diabetes management.[9] However, it is important to select patients for such regimens carefully. These regimens are difficult to learn, involve multiple injections, frequent blood glucose measurements, and require considerable increased resources. Such management has also resulted in more hypoglycaemic events and increases in body weight.[1] The hypoglycaemic event rates in the present study have been previously reported.[9] Severe hypoglycaemia (overall incidence 22 events in 100 patient years) in log-linear regression analysis was only associated with younger age and lower HbA_{1c}, not injection frequency. This weight gain, an undesirable by-product of a strict regimen,[33] might influence the typical teenager's compliance or adherence.[34] Girls in particular may omit insulin doses in attempts to control weight.[35,36] Selected candidates for intensive diabetes management, therefore, are highly motivated, have no needle-phobia, good family and friend support[37] and excellent diabetes education. By contrast, adolescents with significant family dysfunction, poor compliance, recurrent diabetic ketoacidosis and severe eating disorders should not be considered suitable candidates for intensive regimens. Thus, poor metabolic control *per se* is not necessarily an indication for a more intensive insulin-therapy regimen. Indeed it is likely that selection of motivated individuals for an intensified regimen (with more short-acting insulin and in-depth education) may explain the better glycaemic control in some of our centres rather than the insulin regimen *per se*. Further analysis of the DCCT results in adolescents[38] suggested that supportive behavioural therapy over a long period of time in compliant patients was the main factor in obtaining good control.

The findings of this study raise some key questions in childhood diabetes. How do we define intensive diabetes management in children? What are the glycaemic targets? What are the optimal injection regimens at different ages? What should be the starting insulin dose and should it be the same in children and adolescents? Can more aggressive insulin treatment at onset prolong the remission phase? What is the patient's self-perceived quality of life, how does this affect glycaemic control, and what is the psychosocial impact of different diabetes regimens on the child?

These questions and conundrums must be resolved in the paediatric setting, as it is now established that better glyceamic control in the adolescent subset[1] and in children[39,40] is related to fewer late complications. In addition, management guidelines and quality assessment programmes need to be developed for childhood and adolescence with a view to reaching optimal metabolic control in a greater proportion of young people with diabetes.

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